REMARKS

I. Introduction

As an initial matter, applicants' representatives, Andrea Small and Christian M. Bauer, wish to thank the Examiner and her supervisor for their time during the telephonic interview of 21 Feb. 2007. During the interview, Mrs. Small and Mr. Bauer discussed proposed claim amendments and the prior art cited in the Final Office Action dated 6 December 2006. The discussion of the claim amendments and the prior art is formalized in the remarks below.

None of the prior art references alone or in combination teach or fairly suggest the claimed invention of a sterile-filtered nanoparticulate dispersion comprising particles of beclomethasone, budesonide, or combinations thereof having tyloxapol adsorbed on the surface thereof. Withdrawal of the rejection in view of the amendments to the claims and the arguments set forth below is respectfully requested.

Receipt of an Office Action dated December 6, 2006, is acknowledged. In the Action, claims 1-14 are rejected as allegedly obvious over Wiedmann *et al.*, U.S. Patent No. 5,747,001 ("Wiedmann"), in view of Tabibi *et al.*, U.S. Patent No. 6,682,758 ("Tabibi"), Osbakken *et al.*, U.S. Patent Application Publication 2002/0061281 ("Osbakken"), or Saidi *et al.*, U.S. Patent No. 6,241,969 ("Saidi").

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the reasons that follow.

II. Status of the Claims

With this amendment (filed concurrently with an RCE) claim 1 is amended to clarify that which the applicants regard as their invention. Claim 1, as amended, is reproduced in its entirety below.

1. A sterile nanoparticulate dispersion comprising:
a) liquid dispersion medium;

b) nanoparticulate beclomethasone particles, nanoparticulate budesonide particles, or a combination thereof dispersed in the dispersion medium, the nanoparticulate beclomethasone and nanoparticulate budesonide particles having an effective average particle size of less than about 150 nm; and

c) tyloxapol as a surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone and/or the nanoparticulate budesonide particles in an amount effective to prevent the aggregation of the nanoparticulate beclomethasone and/or budesonide particles,

wherein the nanoparticulate composition is sterile filtered with a filter having a pore size of 0.2 μm or less.

Support for the nanoparticulate composition in the form of a dispersion is found throughout the application, and specifically at paragraph [0072] of the published application. This paragraph provides a method of forming the dispersion: "milling of the aqueous beclomethasone or budesonide to obtain a nanoparticulate dispersion comprises . . . ."

Support for the composition in the form of a dispersion comprising a liquid dispersion medium is found at paragraph [0073]: "The liquid dispersion medium can be any medium in which the active particles are poorly soluble."

Support for the amendment clarifying that the tyloxapol is "in an amount effective to prevent the aggregation of the nanoparticulate beclomethasone and/or budesonide particles," is found at paragraph [0044].

Additionally, claims 2-14 have been amended to correct for antecedent basis.

No new matter has been added.

Claims 1-14 are under examination.

III. The Invention

The present invention is directed to a nanoparticulate dispersion of beclomethasone, budesonide, or combinations thereof dispersed in a liquid dispersion medium. These nanoparticles are characterized by their size, i.e., at least 50% of the particles have a weight average particle size of less than about 150 nm when measured by techniques known to those

skilled in the art as described at paragraph [0057]. One of ordinary skill in the art would therefore distinguish a nanoparticle dispersion of an active ingredient from a solution of the active ingredient. In a solution, the active ingredient is dissolved such that there are no "particles" of the active ingredient. In a solution, the interaction between the active ingredient and the solvent is on a molecular level.

A surface stabilizer, tyloxapol, is included in the claimed nanoparticulate dispersion. Tyloxapol is adsorbed on the surface of the nanoparticles, or in other words, the tyloxapol is physically adhered to the surface of the nanoparticles to prevent aggregation of the particles. See e.g., [0012].

The present invention is also directed to a nanoparticulate dispersion that has been sterile filtered. As the passage at paragraph [0018] suggests, the applicants submit that the state of the art for sterile filtration, which typically requires passing the composition through a filter having a pore size of less than or equal to 0.2-microns to remove bacteria, is typically not used to sterilize conventional suspensions of microsized drug particles. This is because the drug substance particles are too large to pass through the pores of the 0.2-micron filter membrane. The inventors of the present application have provided examples 5-9 to illustrate this problem.

IV. Rejection of the Claims Under 35 U.S.C. § 103

The Final Office Action cites Wiedmann (U.S. Patent No. 5,747,001), Tabibi (US Patent No. 6,682,758), Osbakken (U.S. Appln. Pub. No. 2002/0061281), and Saidi (U.S. Patent No. 6,241,969) in support of the obviousness rejections.

As noted by the Examiner during the interview, the rejection cites Wiedmann as teaching every element of the claim except for the element: "wherein the nanoparticulate composition is sterile filtered." The secondary references were cited as teaching the conventional use of sterile filtration of beclomethasone and/or budesonide compositions.

None of the prior art references alone or in combination teach or fairly suggest the claimed invention of sterile-filtered nanoparticulate dispersion comprising particles of

beclomethasone, budesonide, or combinations thereof having tyloxapol adsorbed on the surface thereof for at least the following reasons.

1. Wiedmann

As noted by the Examiner in the Final Office Action rejection, Wiedmann is directed to a process of making nanoparticle beclomethasone aerosols, which process includes attrition and filtration. See col. 7, lines 18-21. The filtration described in the passage cited by the Office Action relates to a coarse filtration using sieves, screens, or the like to separate the grinding media from the liquid dispersion. It is unclear how this passage relates to using filtration to sterilize a composition, particularly in view of the Examiner's acknowledgement: "Wiedmann lacks a teaching on sterile filtration" (Page 2 of the Final Office Action dated 6 Dec. 2005).

Accordingly, there is no teaching or suggestion in Wiedmann of sterile filtering a nanoparticulate dispersion comprising particles of beclomethasone, budesonide, or combinations thereof having tyloxapol adsorbed on the surface thereof.

2. Tabibi

Tabibi fails to provide the motivation to sterile filter the composition of Wiedmann. Tabibi is directed to an emulsion where a water insoluble active agent is dissolved in a water-miscible organic solvent, and the water-miscible organic solvent forms vesicles when combined with water. See col. 2, lines 53-59. These vesicles of organic solvent are characterized as having an average particle size. See col. 7, lines 32-34. Organic vesicles containing a dissolved active agent in solution are not the same as the nanoparticulate beclomethasone aerosol of Wiedmann or the nanoparticulate dispersion of beclomethasone and/or budesonide of the claimed invention.

Tabibi describes using a 0.2-micron filter to sterilize its compositions, but its compositions are active agents dissolved in solution. There is no teaching or suggestion in Tabibi to sterile filter a nanoparticulate composition, let alone a nanoparticulate beclomethasone aerosol taught in Wiedmann. Therefore, the combination of Wiedmann and Tabibi fails to teach or fairly suggest the claimed invention of a sterile filtered,

nanoparticulate dispersion comprising particles of beclomethasone, budesonide, or combinations thereof having tyloxapol adsorbed on the surface thereof.

3. Osbakken

Osbakken also fails to provide the motivation to sterile filter the composition of Wiedmann. Osbakken is directed to aerosol administration of active agents to the nasal cavities of a subject for the treatment of sinusitis. Paragraph [0138]-[0141] list steroidal anti-inflammatory compounds useful in the invention, including beclomethasone and budesonide. Paragraphs [0171]-[0208] describe fourteen examples. All of the active agents provided in the examples are dissolved in solution. Moreover, none of these examples include beclomethasone or budesonide. The only steroidal anti-inflammatory compound provided is described in the 11th example at paragraphs [0198]-[0200]. It is betamethasone, and it is dissolved in sterile water.

Osbakken does teach the use of a 0.2-micron filter to sterile its formulations, but "the ingredients of such formulations will generally be dissolved in a solvent such as water or saline solution." [0104]. There is no teaching or suggestion in Osbakken to sterile file a nanoparticulate composition, let alone a nanoparticulate beclomethasone aerosol as taught in Wiedmann. Therefore, the combination of Wiedmann and Osbakken fails to teach or fairly suggest the claimed invention of a sterile filtered, nanoparticulate dispersion comprising particles of beclomethasone, budesonide, or combinations thereof having tyloxapol adsorbed on the surface thereof.

4. Saidi

Saidi also fails to provide the motivation to sterile filter the composition of Wiedmann. Saidi is directed to compositions of corticosteroids in a dissolved state. See Abstract. Moreover, Saidi suggests that acceptable cosolvents may be added to the steroidal composition to increase the solubility of the corticosteroid. Col. 5, lines 15-18.

Similar to Tabibi and Osbakken, and as cited by the Examiner, Saidi does sterilize its compositions by passing them through a 0.2-micron filter. It compositions, like Tabibi and

Osbakken, are solutions. There is no teaching or suggestion in Saidi to sterile filter a nanoparticulate composition, let alone a nanoparticulate beclomethasone aerosol as taught in Wiedmann. Therefore, the combination of Wiedmann and Saidi fails to teach or fairly suggest the claimed invention of a sterile filtered, nanoparticulate dispersion comprising particles of beclomethasone, budesonide, or combinations thereof having tyloxapol adsorbed on the surface thereof.

Accordingly, none of the secondary references, Tabibi, Osbakken, or Saidi provide motivation to sterile filter a nanoparticulate beclomethasone aerosol of Wiedmann. Therefore, the Final Office Action rejection does not teach or fairly suggest the claimed invention of a sterile filtered, nanoparticulate dispersion comprising particles of beclomethasone, budesonide, or combinations thereof having tyloxapol adsorbed on the surface thereof. Withdrawal of the rejection is respectfully requested and early notice of the allowance of the claims is greatly appreciated.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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